

REMARKS

**1. Interview with Examiner**

The helpfulness and courtesies extended by the Examiner during the telephonic interview of 23 February 2006 are greatly appreciated. At that time, various proposed amendments to the claims were discussed, substantially the same as reflected in the present amendment. Applicant's representative urged that the proposed amendments overcome the various rejections under 35 USC 112, first paragraph. The Examiner agreed at the end of the interview to also reevaluate the prior art rejections in view of the proposed claim amendments. In a subsequent telephone conversation, the Examiner advised the undersigned that the proposed claim amendments would not overcome the prior art rejections, so additional arguments and/or evidence would need to be submitted to rebut the obviousness rejection.

**2. Status of the Claims**

As noted above, the claims have been amended substantially as proposed during the interview. Additional amendments have been made to obviate some particular concerns, such as deleting the language, "such as..." from some of the claims and eliminating the use of the word "analogue" in some of the dependent claims since that term has been removed from independent claim 133.

A "clean" copy of the claims as amended is enclosed.

**3. Information Disclosure Statement**

The Examiner has indicated that he was unable to find the references by Ortega et al. and Karlin et al. that were listed on page 11 of the Information Disclosure Statement submitted on June 15, 2005, and that the year of publication for those references was not indicated on the PTO

Form 1449. In response thereto, enclosed is a new Form 1449 which provides a full citation for each of the publications, and a copy of each publication is enclosed.

**4. Rejections Under 35 USC 112, First Paragraph – Written Description**

The Examiner has rejected the claims for reasons set forth in paragraphs D4 – 7 on pages 3-5 of the Office Action. These rejections are respectfully traversed.

Claims 92 has been amended to delete the language objected to by the Examiner.

Claim 133 and the relevant dependent claims have been amended to replace the term “analogue” with the term “T<sub>H</sub> epitope-containing” as a means of referring to the modified IL-5 polypeptides utilized in the method of the invention. It is believed that these amendments obviate the Examiner’s objection, and it appeared that the Examiner was in agreement during the interview.

Claims 73-75 have been cancelled, thereby obviating those objections.

Claim 85 has been objected to with the Examiner urging that there is a “lack of written description regarding method of using IL-5 with specified locations for modifications”.

However, claim 85 particularly defines that the foreign T<sub>H</sub> epitope is provided “in at least one of loops 1-3 or in the amino acid residue C-terminal to helix D”, with further reference to Fig. 3 of the application for human and murine IL5. Applicant submits that this language is fully supported by the specification, and would be well understood by those skilled in the art. It appears that the Examiner was in agreement during the interview.

In view of the above, reconsideration and withdrawal of the rejections are requested.

**5. Rejections of the Claims Under 35 USC 112, First Paragraph – Enablement**

Various claims have been rejected for alleged lack of enablement for the reasons set forth in paragraphs E.5-9 on pages 6-9 of the Office Action. These rejections are respectfully traversed.

Several of the rejections are essentially duplicative with rejections of the same claims for essentially the same reasons for alleged lack of written description. Those rejections, Applicant submits, have been overcome for the reasons discussed above.

Claim 100 has been rejected for alleged claim of enablement regarding “a method for treating asthma or chronic allergic conditions characterized by eosinophilia”.

First of all, with respect to the term “treating”, Applicant submits that this language is well understood and well accepted as appropriate claim terminology for method of treatment claims of the type in the present application. Moreover, claim 100 further defines the method as administering “to a patient in need thereof an immunogenically effective amount” of at least one of the T<sub>H</sub> epitope-containing Il-5 polypeptides of the invention. Again, such language is standard acceptable method of treatment claim language.

During the interview, the Examiner questioned the understanding in the art with respect to the relationship of eosinophilia and Il-5 activity. In that regard, the Examiner is referred to page 4, line 31 through page 5, line 27 of the present specification which discusses the knowledge in the art of this aspect, and refers to various prior art publications that discuss that knowledge.

During the interview the Examiner also questioned the understanding in the art of the term “artificial MHC-II binding peptide sequences”. The “artificial” sequences are simply ones

that are not found in nature (or, has not yet been identified in nature). Examples of such sequences are the so-called "PADRE" sequences noted on pages 30-31 of the specification and disclosed in WO 95/07707.

As such, Applicants submit that the claims are indeed fully enabled to one skilled in the art, so that the rejection should be withdrawn.

## **6. Rejections Over Prior Art**

The claims have been rejected under 35 USC 103 for obviousness over a combination of Dalum et al. in view of Steinaa et al., and further in view of Foster et al., and over a combination of Dalum et al., in view of Mouritsen et al., and further in view of Foster et al. These rejections are respectfully traversed. Reconsideration and withdrawal thereof are requested.

### **6.1 Summary of the Invention**

As recited most broadly in independent claims 100 and 133, the present invention is directed to a method of treatment which comprises administering a modified version of an animal's autologous IL-5 polypeptide, wherein the modified version contains at least one foreign T<sub>H</sub> epitope, whereby immunization with the T<sub>H</sub> epitope-containing IL-5 polypeptide causes the animal to produce antibodies against the animal's autologous IL-5 polypeptide.

### **6.2 The Examiner's Combination of References**

None of the references cited by the Examiner individually teaches Applicant's claimed method. Instead, the Examiner has combined several different references and urged that a combination of the references renders Applicant's claims *prima facie* obvious.

In particular, the Examiner urges that Foster et al. "show that IL-5 knock out mice exhibit decreased eosinophilia..., firmly establishing a roll for IL-5 in promoting eosinophilia and

airway inflammation” which, in the Examiner’s opinion, “would provide motivation to a person of ordinary skill in the art to inhibit IL-5 as a method of treating eosinophilia and airway inflammation”. But the Examiner recognizes that Foster et al. do not describe any modified IL-5 polypeptides which contain foreign T<sub>H</sub> epitopes. For that teaching, the Examiner relies upon the references to Dalum et al. and Mouritsen et al. which do not disclose any IL-5 polypeptides, but described that “autotolerance of self-proteins can be overcome by introducing a T<sub>H</sub> epitope(s) into self-proteins”.

### **6.3 Arguments Against the Examiner’s Prima Facie Case of Obviousness**

#### *A. The Examiner Has Not Properly Established a Prima Facie Case of Obviousness*

The essence of the Examiner’s rejection is an assumption that one of ordinary skill in the art would be motivated by the teachings of Foster et al. to modify the IL-5 polypeptides of Dalum et al. and Mouritsen et al. to include foreign T<sub>H</sub> epitopes with a reasonable expectation of success that the modified IL-5 polypeptides would produce autotolerance against the autologous IL-5 polypeptides. But Applicants submit that one skilled in the art would not be so motivated, and would, in either event, not have a reasonable expectation of success based upon all of the teachings and the prior art.

In particular, another article by Dalum et al. (Dalum et al. 1996, attached hereto as Exhibit 1) shows that introduction of an epitope does not necessarily render a molecule immunogenic. Figure 2, panel F, of the publication shows that BALB/k mice immunized with an ubiquitin variant (including the Hel epitope) did not produce anti-ubiquitin antibodies. Thus, even though Dalum et al. (1996) demonstrates that immunogenic variants can be made, the results are not so predictable contrary to the suggestion of the Examiner.

*B. Any Prima Facie Case of Obviousness is Rebutted By a Showing of Unexpected and Improved Results*

It is a well established principle in patent law that a *prima facie* case of obviousness can be rebutted by a showing of secondary considerations, including evidence of unexpectedly improved results for the claimed invention as compared to the closest prior art. This principle has been established in a long line of cases, perhaps beginning with the decision of *In re Papesch*, 137 USPQ 43 (CCPA 1963).

Under these well established principles, a *prima facie* case of obviousness shifts the burden to the applicant to rebut the rejection with evidence, namely evidence to support a conclusion of non-obviousness. When such evidence is submitted, the Examiner must reevaluate any such rejection in light of all of the evidence. In essence, “if rebuttal evidence of adequate weight is produced, the holding of *prima facie* obviousness, being but a legal inference from previously uncontradicted evidence, is dissipated.” *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cert. 1984).

Following this line of cases, the present Applicant can then rebut the Examiner’s alleged *prima facie* case of obviousness by showing improved results as compared to the closest prior art. But in considering that evidence, it is important to remember that it is only necessary for the Applicant to show improved results as compared to “the closest compounds actually taught in the reference” and not as compared against some theoretical compounds that are not specifically taught in the cited references. *Ex Parte Westphal et al.*, 223 USPQ 630, 633 (USPTO Bd. Pat. App. & Int. 1983).

Thus, in the present application, Applicant can rebut the Examiner’s *prima facie* case of obviousness by showing improved results for the present invention as compared to the actual

examples taught in the closets references cited by the Examiner, namely the closest examples actually taught in the Foster et al., Dalum et al., or Mouritsen et al. references.

With respect to Dalum et al. and Mouritsen et al., these references, as admitted by the Examiner, do not describe any IL-5 polypeptides which contain T<sub>H</sub> epitopes. Thus, whatever those references might teach about autotolerance to self-proteins, they do not describe any polypeptides which would cause *in vivo* down-regulation of IL-5 activity or would induce an animal to produce antibodies against the animal's autologous IL-5 polypeptide.

With respect to Foster et al., that reference only teaches autologous IL-5 polypeptides, and does not describe any modified IL-5 analogues. It is well understood, and has been for some time, that self-proteins (such as described by Foster et al.) are non-immunogenic in the autologous host. That of course is the underlying basis and need for the present invention, which is not at all discussed or suggested in Foster et al. For example, the Hertz et al. 2001 publication (attached hereto as Exhibit 2) clearly shows that wild-type murine IL-5 is non-immunogenic (see for example the results described in figures 2A and 2B).

The modified IL-5 polypeptides of the present invention, on the other hand, have been shown to effectively cause *in vivo* down-regulation of IL-5 activity and to induce production of antibodies against autologous IL-5. In particular, examples 19 and 20 in the present application describe two different IL-5 variants according to the invention which were shown to be immunogenic in mice and to produce an effect on eosinophilia. In addition, the later publication by Hertz et al. (attached Exhibit 2), which includes as a co-author the present inventor Steen Klysner, describes another IL-5 variant which also is shown to be immunogenic and to produce an effect on eosinophilia.

Thus, IL-5 variants according to the present invention, containing a foreign T<sub>H</sub> epitope, have been shown to be immunogenic (to produce antibodies against autologous IL-5) and have been shown to have the desired effect on eosinophilia; whereas the polypeptides described in the Examiner's Dalum et al., Mouritsen et al., and Foster et al. publications would not be immunogenic against IL-5, would not result in down-regulation of IL-5 activity, would not result in the product of antibodies against autologous IL-5, and would not have an effect on eosinophilia. Such a comparison can only lead to a conclusion the IL-5 variants of the present invention provide unexpectedly improved results as compared to any of the polypeptides described in the Examiner's cited references. Applicants submit that this kind of showing, following the well established principles for rebutting *prima facie* obviousness, clearly rebuts and overcomes the Examiner's *prima facie* obviousness rejection.

**7. Conclusion**

In view of the above, reconsideration and withdrawal of the rejections and early allowance of all the claims is requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicant petitioned for an extension of three months to March 14, 2006 for the period in which to file a response to the Office Action dated September 14, 2005 in the concurrently filed Notice of Appeal. The required fee has been paid in connection with the proper filing of this Notice of Appeal.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By

  
Leonard R. Svensson, #30,330

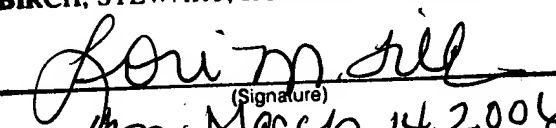
LRS/lmt  
4614-0109P

P.O. Box 747  
Falls Church, VA 22040-0747  
(703) 205-8000

Attachment(s)

**I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on: March 14, 2006**  
(Date of Deposit)

**BIRCH, STEWART, KOLASCH & BIRCH, LLP**

  
(Signature)  
March 14, 2006  
(Date of Signature)